

FORM PTO 1390
(REV 5-93)

US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NUMBER
2001_1692A

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. §371

U.S. APPLICATION NO.
(if known, enter 37 CFR 1.6)
NEW 10/009835

International Application No.
PCT/JP00/03923

International Filing Date
June 16, 2000

Priority Date Claimed
June 18, 1999

Title of Invention
QUICKLY DISINTEGRATING SOLID PREPARATIONS

Applicant(s) For DO/EO/US
Kazuhiro OHKOUCHI and Hiroyoshi KOYAMA


Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. §371(c)(2)). **ATTACHMENT A**
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3)).
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19.
9. ☒ An executed oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)). **ATTACHMENT B**
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. **ATTACHMENT C**
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
ATTACHMENT D
13. ☐ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ Other items or information:

THE COMMISSIONER IS AUTHORIZED
TO CHARGE ANY DEFICIENCY IN THE
FEE FOR THIS PAPER TO DEPOSIT
ACCOUNT NO. 23-0975.

U.S. APPLICATION NO. (of known prior U.S. application) NEW 10/009835		INTERNATIONAL APPLICATION NO. PCT/JP00/03923		ATTORNEY'S DOCKET NO. 2001 1692A	
15. <input checked="" type="checkbox"/> The following fees are submitted				CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37-CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee nor international search fee paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 International Search Report has been prepared by the EPO or JPO \$ 890.00 International preliminary examination fee not paid to USPTO but international search paid to USPTO \$ 740.00 International preliminary examination fee paid to USPTO but claims did not satisfy provisions of PCT Article 33(1)-(4) \$ 690.00 International preliminary examination fee paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$ 100.00				\$890.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$890.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	32 -20 =	12	X \$18.00	\$216.00	
Independent Claims	- 3 =		X \$84.00	\$	
Multiple dependent claim(s) (if applicable)			+ \$280.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$1,106.00	
<input type="checkbox"/> Small Entity Status is hereby asserted. Above fees are reduced by 1/2.				\$	
SUBTOTAL =				\$1,106.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+ \$	
TOTAL NATIONAL FEE =				\$1,106.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40 per property +				\$40.00	
TOTAL FEES ENCLOSED =				\$1,146.00	
a. <input checked="" type="checkbox"/> A check in the amount of <u>\$1,146.00</u> to cover the above fees is enclosed. A duplicate copy of this form is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. 23-0975 in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>23-0975</u> .				Amount to be refunded \$ Amount to be charged \$	
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
19. CORRESPONDENCE ADDRESS <div style="text-align: center;">  000513 PATENT TRADEMARK OFFICE </div>			By: <u>Warren M. Cheek, Jr.</u> Warren M. Cheek, Jr. Registration No. 33,367 WENDEROTH, LIND & PONACK, L.L.P. 2033 "K" Street, N.W., Suite 800 Washington, D.C. 20006-1021 Phone: (202) 721-8200 Fax: (202) 721-8250 December 17, 2001		

QUICKLY DISINTEGRATING SOLID PREPARATIONS

TECHNICAL FIELD

5 The present invention relates to solid preparations that disintegrate quickly in the presence of saliva or a small amount of water in the oral cavity, particularly those useful as intraorally disintegrating solid preparations.

10 BACKGROUND ART

For aged people and children who are difficult to swallow drugs, solid preparations that disintegrate or dissolve quickly in the oral cavity have long been developed. For example, an intraorally disintegrating
15 tablet preparation is described in the International Publication No. WO93/12769, which is obtained by suspending a drug, lactose, and mannitol in aqueous agar solution, filling the resulting suspension in a molding pocket or the like, and drying the molding under reduced
20 pressure. This molding shows quick disintegration but is more fragile than usual tablets so that it is readily cracked, chipped, etc. and a long time is required for its production; thus the process for production is poor in productivity. In Japanese Patent Laying-Open No.6-
25 218028(1994) and Japanese Patent Laying-Open No.8-

19589(1996), a process for production of a tablet preparation is described, where moist powder after kneading is filled in the tablet molding well for wet shaping followed by drying. The resulting tablet preparation, being porous and having a moderate void fraction, shows quick disintegration. However the industrial productivity of this process for production is poor because a wet material with low fluidity is filled and compressed so that the amount filled in each well varies greatly and a special dryer is necessary.

Then a few processes for production of an intraorally disintegrating tablet preparation by dry tableting excellent in productivity have also been reported. For example, a process for production of an intraorally disintegrating tablet preparation by dry tableting using a saccharide with a good moldability and a saccharide with a poor moldability in combination is described in the International Publication No. WO95/20380. Also a process for production of an intraorally disintegrating tablet preparation by dry tableting using granules obtained by wet or dry granulation using an excipient and erythritol, a sugar alcohol, in combination is described in the International Publication No. WO98/02185.

In addition, a process for production of a tablet

preparation that disintegrates quickly in the oral cavity, by combining a saccharide or a sugar alcohol having a mean particle diameter of not more than 30 μm , an active ingredient, and a disintegrating agent is described in the International Publication No. WO97/47287. According to this process, the molding obtained by pulverization of a saccharide or a sugar alcohol, such as D-mannitol or lactose, followed by addition of a disintegrating agent, etc. and compression molding shows quick disintegration, whereas when coarse particles of a saccharide (lactose, mean particle diameter of 80 μm) or a sugar alcohol (D-mannitol, mean particle diameter of 60 μm) before pulverization are used, molding is difficult under a low tabletting pressure and even the molding obtained under a high tabletting pressure does not show a sufficient mechanical hardness.

D-mannitol is known to produce a very high friction (binding) at the surface of the mortar wall during compression molding. In addition, pulverization is undesirable not only because it strengthens the friction at the surface of the mortar wall but also from the viewpoint of handling because it reduces fluidity during the production of the tablet preparation (Summary of lectures at the 14th Symposium on Particulate Preparations and Designs, p.115 (1997), Handbook of Pharmaceutical

Excipients 2nd Ed., p.294 (1994), The Pharmaceutical Press).

DISCLOSURE OF THE INVENTION

5 The inventors have conducted extensive studies on
intraorally disintegrating tablet preparations that can
be industrially produced with common installations
without requiring any special manufacturing technique.
As the result of the studies, the inventors found that an
10 intraorally disintegrating tablet preparation that has a
practically not problematic hardness, disintegrates
quickly, and has no problem in productivity can be
obtained by dry tableting even under a low compression
pressure when an active ingredient is combined with a
15 relatively coarse powder of a saccharide or a sugar
alcohol, a disintegrating agent, and a cellulose compound.
As a result of further studies, the inventors have
completed the present invention. That is, the invention
relates to:

20 (1) a quickly disintegrating solid preparation
comprising a) an active ingredient, b) a saccharide or a
sugar alcohol with the mean particle diameter of 30 μm to
300 μm (not less than 30 μm and not more 300 μm), c) a
disintegrating agent, and d) a cellulose compound;

25 (2) the preparation according to the above-mentioned (1),

wherein the preparation is an intraorally quickly disintegrating solid preparation;

(3) the preparation according to the above-mentioned (1), wherein the preparation is a tablet preparation;

5 (4) the preparation according to the above-mentioned (1), wherein 40 to 95 parts of a saccharide or a sugar alcohol is contained in 100 parts of the solid preparation by weight;

10 (5) the preparation according to the above-mentioned (1), wherein 0.5 to 15 parts of a disintegrating agent is contained in 100 parts of the solid preparation by weight;

15 (6) the preparation according to the above-mentioned (1), wherein 0.5 to 40 parts of a cellulose compound is contained in 100 parts of the solid preparation by weight;

20 (7) the preparation according to the above-mentioned (1), wherein the saccharide is one or more saccharides selected from the group consisting of glucose, fructose, lactose, sucrose, and trehalose;

(8) the preparation according to the above-mentioned (1), wherein the saccharide is lactose;

25 (9) the preparation according to the above-mentioned (1), wherein the sugar alcohol is one or more sugar alcohols selected from the group consisting of D-mannitol,

erythritol, xylitol, maltitol, and sorbitol;

(10) the preparation according to the above-mentioned (1),
wherein the sugar alcohol is D-mannitol;

(11) the preparation according to the above-mentioned (1),
5 characterized in that D-mannitol with the mean particle
diameter of 30 μm to 300 μm is used as the saccharide or
sugar alcohol with the mean particle diameter of 30 μm to
300 μm ;

(12) the preparation according to the above-mentioned (1),
10 wherein the disintegrating agent is one or more
disintegrating agents selected from the group consisting
of carmellose calcium, carboxymethylstarch sodium,
croscarmellose sodium, and crospovidone;

(13) the preparation according to the above-mentioned (1),
15 wherein the cellulose compound is one or more substances
selected from the group consisting of crystalline
cellulose, powder cellulose, low substituted
hydroxypropylcellulose, and carmellose;

(14) the preparation according to the above-mentioned (1),
20 wherein the active ingredient is manidipine
hydrochloride;

(15) the preparation according to the above-mentioned (1),
wherein the active ingredient is voglibose;

(16) the preparation according to the above-mentioned (1),
25 wherein the active ingredient is candesartan cilexetil;

(17) the preparation according to the above-mentioned (1), wherein the active ingredient is pioglitazone hydrochloride;

(18) the process for production of the preparation according to the above-mentioned (1), characterized in that a mixture containing a) an active ingredient, b) a saccharide or sugar alcohol with the mean particle diameter of 30 μm to 300 μm (not less than 30 μm and not more than 300 μm), c) a disintegrating agent, and d) a cellulose compound is molded by compression;

(19) a quickly disintegrating solid preparation containing a) an active ingredient, b-1) a saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm (not less than 5 μm and below 90 μm), b-2) a saccharide or a sugar alcohol with the mean particle diameter of 90 μm to 500 μm (not less than 90 μm and not more than 500 μm), c) a disintegrating agent, and d) a cellulose compound;

(20) the preparation according to the above-mentioned (19), containing 0.1 to 10 parts of the ingredient b-2) per 1 part of the ingredient b-1) by weight;

(21) the preparation according to the above-mentioned (19), characterized in that a mixture of the ingredient b-1) and the ingredient b-2) as the ingredient b-1) and the ingredient b-2);

(22) the preparation according to the above-mentioned (21), wherein the mean particle diameter of the mixture is 30 μm to 300 μm (not less than 30 μm and not more than 300 μm);

5 (23) the preparation according to the above-mentioned (19), wherein the mean particle diameter of the ingredient b-1 is 30 μm to below 90 μm (not less than 30 μm and below 90 μm);

10 (24) the preparation according to the above-mentioned (19), wherein the mean particle diameter of the ingredient b-1 is 35 μm to 80 μm (not less than 35 μm and not more than 80 μm);

15 (25) the preparation according to (19), wherein the mean particle diameter of the ingredient b-2) is 90 μm to 300 μm (not less than 90 μm and not more than 300 μm);

(26) the preparation according to the above-mentioned (19), wherein the mean particle diameter of the ingredient b-2) is 90 μm to 200 μm (not less than 90 μm and not more than 200 μm);

20 (27) the preparation according to the above-mentioned (19), wherein the saccharide is one or more saccharides selected from the group consisting of glucose, fructose, lactose, sucrose, and trehalose;

25 (28) the preparation according to the above-mentioned (19), wherein the saccharide is lactose;

(29) the preparation according to the above-mentioned (19), wherein the sugar alcohol is one or more sugar alcohols selected from the group consisting of D-mannitol, erythritol, xylitol, maltitol, and sorbitol;

5 (30) the preparation according to the above-mentioned (19), wherein the sugar alcohol is D-mannitol;

(31) the preparation according to the above-mentioned (19), characterized in that D-mannitol with the mean particle diameter of 30 μm to 90 μm and D-mannitol with the mean
10 particle diameter of 90 μm to 300 μm are used as the ingredient b-1) and the ingredient b-2), respectively;

(32) the process for production of a preparation according to the above-mentioned (19), characterized in that a mixture containing a) an active ingredient, b-1) a
15 saccharide or a sugar alcohol with the mean particle diameter of 5 μm to below 90 μm (not less than 5 μm and below 90 μm), b-2) a saccharide or a sugar alcohol with the mean particle diameter of 90 μm to 50 μm (not less than 90 μm and not more than 500 μm), c) a disintegrating
20 agent, and d) a cellulose compound is molded by compression; etc.

Active ingredients used in the present invention may be in any form, i.e. solid, crystal, oil, or solution, and one or more agents selected from the group consisting
25 of, for example, alimentary roborants, antipyretic

analgesic antiphlogistics, psychotropic agents,
 anxiolytics, anti-depressants, hypnotic sedatives,
 antispasmodics, central nervous system acting drugs,
 cerebral metabolism improving agents, cerebral
 5 circulation improving agents, antiepileptics,
 sympathomimetics, digestives, antacids, antiulcer agents,
 antitussive expectorants, antiemetics, respiratory
 stimulants, bronchodilators, antiallergic agents, dental
 stomatic agents, anti-histamines, cardiacs,
 10 antiarrhythmic agents, diuretics, hypotensive agents,
 angiotonics, coronary vasodilators, peripheral
 vasodilators, antihyperlipemic drugs, cholagogues,
 antibiotics, chemotherapeutics, antidiabetic agents,
 osteoporosis treating drugs, antirheumatics, skeletal
 15 muscle relaxants, antispasmodic drugs, hormone drugs,
 alkaloid narcotics, sulfa drugs, gout treating agents,
 anticoagulants, antineoplastic agents, and the like are
 used.

Alimentary roborants include vitamins such as
 20 vitamin A, vitamin D, vitamin E (d- α -tocopherol acetate,
 etc.), vitamin B1 (dibenzoyl thiamine, fursultiamine
 hydrochloride, etc.), vitamin B2 (riboflavin butyrate,
 etc.), vitamin B6 (pyridoxine hydrochloride, etc.),
 vitamin C (ascorbic acid, sodium L-ascorbate, etc.), and
 25 vitamin B12 (hydroxocobalamin acetate, cyanocobalamin,

etc.), minerals such as calcium, magnesium, iron, etc., protein, amino acids, oligosaccharides, crude drugs, and the like.

Antipyretic analgesic antiphlogistics include
 5 aspirin, acetaminophen, ethenzamide, ibuprofen,
 diphenhydramine hydrochloride, chlorpheniramine dl-
 maleate, dihydrocodeine phosphate, noscapine,
 methylephedrine hydrochloride, phenylpropanolamine
 hydrochloride, caffeine, anhydrous caffeine, serrapeptase,
 10 lysozyme chloride, tolfenamic acid, mefenamic acid,
 diclofenac sodium, flufenamic acid, salicylamide,
 aminopyrine, ketoprofen, indometacin, bucolome,
 pentazocine, and the like.

Psychotropic agents include chlorpromazine,
 15 reserpine, and the like. Anxiolytics include alprazolam,
 chlordiazepoxide, diazepam, and the like.

Antidepressants include imipramine, maprotilline
 hydrochloride, amphetamine, and the like. Hypnotic
 sedatives include estazolam, nitrazepam, diazepam,
 20 perlapine, phenobarbital sodium, and the like.

Antispasmodics include scopolamine hydrobromide,
 diphenhydramine hydrochloride, papaverine hydrochloride,
 and the like. Central nervous system acting agents
 include citicoline, and the like. Cerebral metabolism
 25 improving agents include meclofenoxate hydrochloride, and

the like. Cerebral circulation improving agents include vinpocetine, and the like. Antiepileptics include phenytoin, carbamazepine, and the like. Sympathomimetics include isopreterenol hydrochloride, and the like.

5 Digestives include stomachic digestives such as diastase, saccharated pepsin, scopolia extract, cellulase AP3, lipase AP, cinnamon oil, etc., and drugs for controlling intestinal function such as berberine chloride, antibiotics-resistant lactic acid bacteriae,
10 lactobacillus bifidus, etc. Antacids include magnesium carbonate, sodium bicarbonate, magnesium aluminometasillicate, synthetic hydrotalcite, precipitated calcium carbonate, magnesium oxide, and the like. Anti-ulcer agents include lansoprazole, omeprazol, rabeprazole, famotidine, cimetidine, ranitidine
15 hydrochloride, and the like.

Antitussive expectorants include chloperastine hydrochloride, dextromethorphan hydrobromide, theophylline, potassium guaiacolsulfonate, guaifenesin,
20 codeine phosphate, and the like. Antiemetics include difenidol hydrochloride, metoclopramide, and the like. Respiratory stimulants include levallorphan tartrate, and the like. Bronchodilators include theophylline, salbutamol sulfate, and the like. Antiallergic agents
25 include amlexanox, seratrodest, and the like.

Dental stomatic agents include oxytetracycline, triamcinolone acetonide, chlorhexidine hydrochloride, lidocaine, and the like.

Antihistamines include diphenhydramine hydrochloride, promethazine, isothipendyl hydrochloride, chlorpheniramine dl-maleate, and the like.

Cardiacs include caffeine, digoxin, and the like.

Antiarrhythmic agents include procainamide hydrochloride, propranolol hydrochloride, pindolol, and the like.

Diuretics include isosorbide, furosemide, hydrochlorothiazide, and the like. Hypotensive agents include derapril hydrochloride, captopril, hydraladine hydrochloride, labetalol hydrochloride, manidipine hydrochloride, candesartan cilexetil, methyldopa, perindopril erbumine, and the like. Angiotonics include phenylephrine hydrochloride, and the like. Coronary vasodilators include carbocromen hydrochloride, molsidomine, verapamil hydrochloride, and the like. Peripheral vasodilators include cinnarizine, and the like.

Antihyperlipemic agents include cerivastatin sodium, simvastatin, pravastatin sodium, atorvastatin calcium hydrate, and the like.

Cholagogues include dehydrocholic acid, trepibutone, and the like.

Antibiotics include cefems such as cefalexin,

cefaclor, amoxicillin, pivmecillinam hydrochloride, cefotiam hexetil hydrochloride, cefadroxil, cefixime, cefditoren pivoxil, cefteteram pivoxil, cefpodoxime proxetil, etc., synthetic ones such as ampicillin, 5 ciclacillin, nalidixic acid, enoxacin, etc., monobactams such as carumonam sodium, penems, carbapenems, and the like.

Chemotherapeutics include sulfamethizole, and the like.

10 Antidiabetic agents include tolbutamide, voglibose, pioglitazone hydrochloride, glibenclamide, troglitazone, and the like.

Osteoporosis treating drugs include ipriflavone, and the like.

15 Skeletal muscle relaxants include methocarbamol, and the like.

Antispasmodic drugs meclizine hydrochloride, dimenhydrinate, and the like.

20 Antirheumatics include methotrexate, bucillamine, and the like.

Hormone drugs include liothyronine sodium, dexamethasone phosphate, predonisolone, oxendolone, leuprorelin acetate, and the like.

25 Alkaloid narcotics include opium, morphine hydrochloride, ipecac, oxycodone hydrochloride, opium

alkaloids hydrochloride, cocaine hydrochloride, and the like.

Sulfa drugs include sulfisomidine, sulfamethizole, and the like.

5 Gout treating drugs include allopurinol, colchicine, and the like.

Anticoagulants include dicoumarol, and the like.

Antineoplastic drugs include 5-fluorouracil, uracil, mitomycin, and the like.

10 Among these, manidipine hydrochloride, voglibose, candesartan cilexetil, pioglitazone hydrochloride, etc., particularly manidipine hydrochloride, are used preferably.

15 The active ingredient may be the one diluted with a diluent used generally in the fields of medicine and foods. An active ingredient after treatment for masking the bitterness of the active ingredient may also be used.

20 The amount of the active ingredient varies depending on the nature and dose of the active ingredient, and is 0.01 to 40 parts, preferably 0.01 to 20 parts, per 100 parts by weight of the solid pharmaceutical preparation of the invention.

25 Saccharides used in the invention include glucose, fructose, lactose, sucrose, trehalose, and the like, among which lactose is used preferably.

Sugar alcohols used in the invention include D-mannitol, erythritol, xylitol, maltitol, sorbitol, and the like, among which D-mannitol is used preferably.

One or more saccharides or one or more sugar alcohols may be used in combination, or a combination of a saccharide and a sugar alcohol may be used.

The mean particle diameter of the saccharide or the sugar alcohol (preferably the sugar alcohol, or more preferably D-mannitol) is 30 to 300 μm (measured by, for example, the laser diffraction particle size analyzer, SYMPATEC Co.: HELOS & RODOS, etc.), preferably above 30 μm , more preferably 31 μm or more, and further more preferably 35 to 200 μm . Saccharides or sugar alcohols of such a particle size are commercially available (Lactose 100M and Lactose 200M of DMV, granulated powder lactose Dilactose R and Dilactose S of Freund Industry Co., Ltd., Tablettose and Flowlac 100 of Meggle Japan, Mannit S and Marinecrystal of Towa Chemical Industry Co., Ltd., 1.05980 of Merck Co., Mannidex of Cerestar Japan, Ltd., Trehalose P of Asahi Chemical Industry Co., Ltd., Sorbitol DP-50M and Amalty MR-50 of Towa Chemical Industry Co., Ltd., Pure Fructose S of Kato Kagaku, and the like). Saccharides and sugar alcohols with the mean particle diameter of 5 to 30 μm are commercially available (Granulac 230 and Solvolac 400 of Meggle Japan,

Mannit P, Xylit P, and Amalty MR-100 of Towa Chemical Industry Co., Ltd., Erythritol (fine powder) of Nikken Chemicals Co., Ltd., and the like). Saccharides and sugar alcohols with the mean particle diameter of 200 to 500 μm are commercially available (Sachelac 80 of Meggle Japan, Trehalose G and Xylitol XC of Asahi Chemical Industry Co., Ltd., Erythritol of Nikken Chemicals Co., Ltd., Anhydrous crystalline glucose TDA-S and Hydrated crystalline glucose TDH of San-ei Sucrochemical Co., Ltd., and the like). In addition, saccharides and sugar alcohols with the mean particle diameter of not less than 500 μm are commercially available (Prismalac 40 of Meggle Japan, Pure Fructose of Kato Kagaku, Amalty MR-20 and Sorbitol DP-10M of Towa Chemical Industry Co., Ltd., and the like). A saccharide or sugar alcohol with the necessary mean particle diameter may be obtained by a method such as pulverization from the commercially available product. Pulverization is performed by using a cutter mill, jet mill, hammer mill, or the like.

A saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm (preferably 30 to below 90 μm) to strengthen the molding may be combined with a saccharide or sugar alcohol with the mean particle diameter of 90 μm to 500 μm (preferably 90 μm to 300 μm) to increase fluidity during manufacturing. In

combination of a fine powder of a saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm (preferably 30 to below 90 μm , more preferably 35 to 80 μm) with a coarse powder of a saccharide or sugar alcohol with the mean particle diameter of 90 μm to 500 μm (preferably 90 μm to 300 μm , more preferably 90 to 200 μm), it is recommendable to use one part of a fine powder of a saccharide or sugar alcohol with 0.1 to 10 parts, preferably 0.2 to 5 parts, of a coarse powder of a saccharide or sugar alcohol by weight. Particularly when the active ingredient is manidipine hydrochloride, it is recommendable to use one part of a fine powder of a saccharide or sugar alcohol usually with 0.2 to 3.5 parts, preferably with 0.3 to 2.5 parts, of a coarse powder of a saccharide or sugar alcohol by weight.

In combination of a fine powder of a saccharide or sugar alcohol with a coarse powder of a saccharide or sugar alcohol, one or more saccharides or one or more sugar alcohols may be combined, or a fine powder of a saccharide or sugar alcohol may be combined with a coarse powder of the same or a different saccharide or sugar alcohol. In addition, a mixture obtained by mixing a fine powder of a saccharide or sugar alcohol with a coarse powder of a saccharide or sugar alcohol may be molded into a quickly disintegrating solid preparation of

the invention, or a fine powder of a saccharide or sugar alcohol and a coarse powder of a saccharide or sugar alcohol are divided into two or more groups to prepare granules, followed by molding into the quickly
5 disintegrating solid preparation of the invention.

When the mixture of a fine powder of a saccharide or sugar alcohol with a coarse powder of a saccharide or sugar alcohol is used as the starting material, the mixture has desirably two or more peaks in the particle
10 size distribution and the mean particle diameter of the mixture is desirably 30 μm to 300 μm .

A desirable combination of a fine powder of a saccharide or sugar alcohol with a coarse powder of a saccharide or sugar alcohol is exemplified by the mixture
15 of D-mannitol with the mean particle diameter of 30 μm to below 90 μm with D-mannitol with the mean particle diameter of 90 μm to 300 μm .

The amount of a saccharide or sugar alcohol used is 40 to 95 parts, preferably 50 to 90 parts, per 100 parts
20 of the solid pharmaceutical preparation by weight.

Disintegrating agents used include carmellose calcium, carboxymethyl starch sodium, croscarmellose sodium, crospovidone, and the like, and 0.5 to 15 parts, preferably 1 to 10 parts, thereof is used per 100 parts
25 of the solid pharmaceutical preparation by weight.

Disintegrating agents are exemplified by
Crospovidone [manufactured by ISP Inc. (USA), BASF
(Germany)], Croscarmellose Sodium (FMC- Asahi Chemical
Industry Co., Ltd.), Carmellose Calcium (Gotoku Yakuhin
5 Co., Ltd.), and Carboxymethylstarch Sodium (Matsutani
Kagaku Co., Ltd., Kimura Sangyo Co., Ltd., etc.).

The crospovidone product may be any cross-linked
polymer that is 1-ethenyl-2-pyrrolidinone homopolymer,
and usually a crospovidone product having a molecular
10 weight of 1,000,000 or more is used. Examples of
commercially available crospovidone products are Cross-
linked Povidone, Kollidon CL [manufactured by BASF
(Germany)], Polyplasdone XL, Xl-10, and INF-10
[manufactured by ISP Inc. (USA)].

15 Cellulose compounds used are crystalline cellulose,
powder cellulose, low substituted hydroxypropylcellulose,
carmellose, and the like, and 0.5 to 40 parts, preferably
1 to 20 parts, thereof is used for 100 parts of the solid
pharmaceutical preparation by weight.

20 Examples of crystalline cellulose products are
CEOLUS KG801, Avicel PH101, PH102, PH301, PH302, and PH-
F20, Avicel RC-A591NF (all manufactured by Asahi Chemical
Industry Co., Ltd.), and the like, including also fine
crystalline cellulose.

25 Examples of low substituted hydroxypropylcellulose

products are low substituted hydroxypropylcellulose of which content of hydroxypropoxyl group is 5 to 16% by weight such as Low Substituted Hydroxypropylcellulose LH11, LH21, LH31, LH22, LH32, LH20, LH30, LH32, and LH33 (all manufactured by Shin-Etsu Chemical Co., Ltd.), and the like. These are commercially available. Low substituted hydroxypropylcellulose can be produced by a publicly known procedure, for example the procedure described in Patent Gazette No.57-53100(1982), or a similar procedure.

Active ingredients, disintegrating agents, and cellulose compounds may be used in combination of one or more of each.

The preparation of the invention may contain a starch product as an excipient such as corn starch, potato starch, wheat starch, rice starch, partially gelatinized starch, gelatinized starch, porous starch, and the like, and various additives used for production of general pharmaceutical preparations, in their respective suitable amounts, unless they interfere with the effect of the invention. Such additives include excipients, binders, sour agents, foaming agents, artificial sweeteners, flavoring agents, lubricants, colorants, stabilizers, pH-modifiers, surfactants, and the like.

Excipients include inorganic excipients such as anhydrous calcium phosphate, precipitated calcium carbonate, calcium silicate, light anhydrous silicic acid, and the like.

5 Binders include hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, powdered acacia, gelatin, pullulan, and the like.

Sour agents include citric acid, tartaric acid, malic acid, ascorbic acid, and the like.

10 Foaming agents include sodium bicarbonate, sodium carbonate, and the like. Sweeteners include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, and the like.

15 Flavoring agents include lemon oil, orange oil, menthol, and the like.

Lubricants include magnesium stearate, sucrose esters of fatty acid, polyethyleneglycol, talc, stearic acid, sodium stearyl fumarate, and the like.

20 Colorants include those for food such as Food Yellow No.5, Food Red No.2, Food Blue No.2, and the like, food lake colorants, ferric oxide, and the like.

Stabilizers include disodium edetate, tocopherol, cyclodextrin, and the like.

25 pH-Modifiers include citrates, phosphates, carbonates, tartarates, fumarates, acetates, amino acid

salts.

Surfactants include sodium lauryl sulfate,
polysorbate 80, hydrogenated oil,
polyoxyethylene(160)polyoxypropylene(30)glycol, and the
5 like.

The particle diameter of these substances is not particularly limited, but the particle diameter is preferably not more than 500 μm not to cause rough feeling in the mouth. These excipients may be used
10 separately or in combination of two or more thereof.

A fine granular nucleus may be used for manufacturing of the solid preparation of the invention, and such a nucleus may be coated with active ingredients and additives etc. followed by further coating by a
15 publicly known procedure for masking of the taste/odor, for enteric coating, for making the preparation into a sustained release form, and for other purposes.

The solid preparation of the invention can be produced either by compression molding of a mixture
20 comprising a) an active ingredient, b) a saccharide or sugar alcohol with the mean particle diameter of 30 μm to 300 μm , c) a disintegrating agent, and d) a cellulose compound, or by compression molding of a mixture comprising a) an active ingredient, b-1) a saccharide or
25 sugar alcohol with the mean particle diameter of 5 μm to

below 90 μm , b-2) a saccharide or sugar alcohol with the mean particle diameter of 90 μm to 500 μm , c) a disintegrating agent, and d) a cellulose compound.

The procedures for production by dividing the starting materials into two groups are exemplified by:

[1] compression molding by mixing a group comprising a) an active ingredient, b-1) a saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm , c) a disintegrating agent, and d) a cellulose compound, and a group comprising b-2) a saccharide or sugar alcohol with the mean particle diameter of 90 μm to 500 μm , c) a disintegrating agent, and d) a cellulose compound, followed by addition of a fluidizing agent, lubricant, sweetener, and/or the like in their respective suitable amounts, as needed;

[2] compression molding by mixing a group comprising a) an active ingredient, b-1) a saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm , and c) a disintegrating agent, and a group comprising b-2) a saccharide or sugar alcohol with the mean particle diameter of 90 μm to 500 μm , c) a disintegrating agent, and d) a cellulose compound, followed by addition of a cellulose compound, fluidizing agent, lubricant, sweetener, and/or the like in their respective suitable amounts as needed;

[3] compression molding by mixing a group comprising a) an active ingredient, b-1) a saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm , b-2) a saccharide or sugar alcohol with the mean particle diameter of 90 μm to 500 μm , c) a disintegrating agent, and d) a cellulose compound as needed, and a group comprising b-1) a saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm , b-2) a saccharide or sugar alcohol with the mean particle diameter of 90 μm to 500 μm , c) a disintegrating agent, and d) a cellulose compound, followed by addition of a cellulose compound, fluidizing agent, lubricant, sweetener, and/or the like in their respective suitable amounts as needed.

The concrete procedures for production include the procedure that an active ingredient and the raw materials of the preparation are mixed in a mixer followed by immediate tableting. Also the procedure that the materials are dry compressed into tablets by the slugging method or roller-compacter method, the procedure for production of granules for tablets by dry tableting using water, acetone, ethyl alcohol, propyl alcohol, or a mixture thereof, in which a binder, if necessary, has been dispersed or dissolved, and the procedure for production of granules for tablets after dividing the

materials into two or more groups may be applicable. For production of tablets from granules for tablets, a cellulose compound, a disintegrating agent, a fluidizing agent, a lubricant, a flavoring agent, a sweetener, and the like may be mixed as needed.

Tablets are molded by using, for example, a single tabletting machine, rotary tabletting machine, and the like. Pressure for tabletting is usually 2.5 to 30 kN/cm². The shape of the solid preparation of the invention is not particularly restricted; the tablet may be round, caplet, doughnut, oblong, etc. or a multilayer tablet, a dry-coated tablet, or the like, and may be covered by coating. The tablet may have marks and letters for identification, and a nick on the surface.

The resultant quickly disintegrating solid preparation, preferably intraorally quickly disintegrating solid preparation, more preferably, intraorally quickly disintegrating tablet of the invention is quickly disintegrated in the oral cavity and has an adequate hardness. It is excellent also in productivity.

Namely, the time required for intraoral disintegration or dissolution (the time till the tablet is completely disintegrated by the action of the saliva in the oral cavity of healthy adult men and women) of the

intraorally quickly disintegrating tablet of the invention varies depending to the size and thickness of the tablet, being normally 5 to 90 seconds, preferably about 5 to 60 seconds. The hardness (measured by the tablet hardness meter) is normally 10 to 200N, preferably about 10 to 150 N.

Therefore the intraorally disintegrating tablet of the invention, like the conventional pharmaceutical preparations containing active ingredients, can be used for treatment and prevention of various diseases as a tablet easy to be taken by patients, aged people, and children who are difficult to swallow the medicine, and as a safe preparation in emergency for general adult people, and is excellent in long-term storage and stability.

The preparation may be orally taken without being disintegrated in the oral cavity, or taken with water. The preparation may also be orally taken after being dissolved in water in a cup or the like.

The Best Mode for Carrying Out the Invention

The invention is explained in more detail with the following Examples and Comparative Examples, though these Examples do not limit the invention.

Examples

The tablet preparations obtained in the Examples and in the Comparative Examples were subjected to the test methods described below for measurement of the hardness and the intraoral disintegration time. Also productivity was assessed based on the observation of fluidity, binding property, and adhesion of powder to the surface of the punch during production of the tablet.

(1) Hardness test

Hardness was measured with the tablet hardness meter (Toyama Sangyo Co., Ltd.). Hardness of each of 5 or 10 tablets was measured, and expressed in the mean of the measurements.

(2) Intraoral disintegration time

The time till disintegration of the tablet in the presence of saliva alone in the oral cavity was measured in 3 healthy adult men (35, 49, and 51 years old).

Example 1

A 40 g portion of manidipine hydrochloride, 303.4 g of D-mannitol (Towa Chemical Industry Co., Ltd.: Mannit S, mean particle diameter of 130 μ m), 50 g of crystalline cellulose (Asahi Chemical Industry Co., Ltd.), 50 g of corn starch (Japan Corn Starch), and 1 g of light anhydrous silicic acid (YKF) were placed in a fluidized

bed granulating dryer (Powrex Co., LAB-1 type), and 139 g of purified water containing 18 g of D-mannitol and 0.6 g of yellow ferric oxide (Anstead) was sprayed, followed by granulating and drying processes, to give granules.

5 To 347 g of the granules, 25 g of crospovidone (ISP Inc.), 1 g of light anhydrous silicic acid, 10 g of magnesium stearate (Taihei Kagaku Sangyo Co. Ltd.), and 1 g of aspartame (Ajinomoto Co. Ltd.) were added, to give a mixed powder.

10 This mixed powder was tabletted into tablets weighing 250 mg each (Kikusui Seisakusho, Correct 12HUK, tablet size of 9.5 mm ϕ , compression pressure of 9.8 kN (1 ton)/cm²).

15 Example 2

 A 180 g portion of manidipine hydrochloride, 495 g of D-mannitol (Merck Co.: 1.05980, mean particle diameter of 45 μ m), 225 g of corn starch, 112.5 g of crystalline cellulose, 2 g of light anhydrous silicic acid, and 56.3 g of crospovidone were placed in a fluidized bed granulating dryer (Powrex Co., FD-3SN type), and 540 g of purified water containing 42.8 g of D-mannitol and 1.4 g of yellow ferric oxide was sprayed, followed by granulating and drying processes, to give granules A.

25 Separately, 872.1 g of D-mannitol (Towa Chemical

Industry Co., Ltd.: Mannit S), 112.5 g of crystalline cellulose, and 56.3 g of crospovidone were placed in a fluidized bed granulating dryer (Powrex Co., FD-3SN type), and 540 g of purified water containing 36.2 g of D-mannitol and 1.4 g of yellow ferric oxide was sprayed, followed by granulating and drying processes, to give granules B.

A 1003 g portion of granules A, 971 g of granules B, 6.3 g of light anhydrous silicic acid, 4.1 g of aspartame, and 41 g of magnesium stearate were mixed.

This mixed powder was tabletted into tablets weighing 250 mg each (Kikusui Seisakusho, Correct 12HUK, tablet size of 9.5 mm ϕ , compression pressure of 4.9, 9.8, and 19.6 kN /cm²).

Example 3

A 90 g portion of manidipine hydrochloride, 416 g of D-mannitol (Merck Co.: 1.05980, mean particle diameter of 45 μ m), 189 g of corn starch, 94.5 g of crystalline cellulose, 1.7 g of light anhydrous silicic acid, and 47.3 g of crospovidone were placed in a fluidized bed granulating dryer (Powrex Co., FD-3SN type), and 423 g of purified water containing 33.5 g of D-mannitol and 0.4 g of yellow ferric oxide was sprayed, followed by granulating and drying processes, to give granules C.

Separately, 884 g of D-mannitol (Towa Chemical Industry Co., Ltd.: Mannit S), 105 g of crystalline cellulose, and 52.5 g of crospovidone were placed in a fluidized bed granulating dryer (Powrex Co., FD-3SN type), and 540 g of purified water containing 35.7 g of D-mannitol and 0.4 g of yellow ferric oxide was sprayed, followed by granulating and drying processes, to give granules D.

A 760 g portion of granules C, 845 g of granules D, 5.1 g of light anhydrous silicic acid, 3.9 g of aspartame, and 33 g of magnesium stearate were mixed.

This mixed powder was tabletted into tablets weighing 210 mg each (Kikusui Seisakusho, Correct 12HUK, tablet size of 9.0 mm ϕ , compression pressure of 9.8 kN/cm²).

Example 4

An 80 g portion of manidipine hydrochloride, 220 g of D-mannitol (Merck Co.: 1.05980, mean particle diameter of 45 μ m), 100 g of corn starch, and 1.2 g of light anhydrous silicic acid were placed in a fluidized bed granulating dryer (Powrex Co., LAB-1 type), and 200 g of purified water containing 6 g of hydroxypropylcellulose (Nippon Soda Co., Ltd.) and 0.4 g of yellow ferric oxide was sprayed, followed by granulating and drying processes,

to give granules E.

Separately, 400.5 g of D-mannitol (Towa Chemical Industry Co., Ltd.: Mannit S), and 100 g of crystalline cellulose were placed in a fluidized bed granulating dryer (Powrex Co., LAB-1 type), and 180 g of purified water containing 16.1 g of D-mannitol and 0.8 g of yellow ferric oxide was sprayed, followed by granulating and drying processes, to give granules F.

A 203.8 g portion of granules E, 258.8 g of granules F, 25 g of crospovidone, 1.4 g of light anhydrous silicic acid, 1 g of aspartame, and 10 g of magnesium stearate were mixed.

This mixed powder was tabletted into tablets weighing 250 mg each (Kikusui Seisakusho, Correct 12HUK, tablet size of 9.5 mm ϕ , compression pressure of 9.8 kN/cm²).

Example 5

A 289 g portion of D-mannitol (Towa Chemical Industry Co., Ltd.: Mannit S), 40 g of crystalline cellulose, 40 g of corn starch, and 1.2 g of light anhydrous silicic acid were placed in a fluidized bed granulating dryer (Powrex Co., LAB-1 type), and 120 g of purified water containing 0.4 g of voglibose and 10 mg of Food Yellow No.5 was sprayed, followed by granulating and

drying processes, to give granules.

To 296 g of the granules, 16 g of crospovidone, 0.32 g of light anhydrous silicic acid, 6.4 g of magnesium stearate, and 0.96 g of aspartame were added, to give a mixed powder.

This mixed powder was tabletted into tablets weighing 200 mg each (Kikusui Seisakusho, Correct 12HUK, tablet size of 9.0 mm ϕ , compression pressure of 9.8 kN/cm²).

Example 6

A 16 g portion of candesartan cilexetil, 273 g of D-mannitol (Towa Chemical Industry Co., Ltd.: Mannit S), 40 g of crystalline cellulose, 40 g of corn starch, and 1.2 g of light anhydrous silicic acid were placed in a fluidized bed granulating dryer (Powrex Co., LAB-1 type), and 120 g of purified water was sprayed, followed by granulating and drying processes, to give granules.

To 296 g of the granules, 16 g of crospovidone, 0.32 g of light anhydrous silicic acid, 6.4 g of magnesium stearate, and 0.96 g of aspartame were added, to give a mixed powder.

This mixed powder was tabletted into tablets weighing 200 mg each (Kikusui Seisakusho, Correct 12HUK, tablet size of 9.0 mm ϕ , compression pressure of 9.8

kN/cm²).

Example 7

A 660 mg portion of pioglitazone hydrochloride, 2670
5 mg of D-mannitol (Towa Chemical Industry Co., Ltd.:
Mannit S), 500 mg of crystalline cellulose, 500 mg of
corn starch, 500 mg of crospovidone, 20 mg of light
anhydrous silicic acid, 100 mg of magnesium stearate, and
50 mg of aspartame were mixed in a tablet bottle.

10 This mixed powder was tabletted into tablets
weighing 250 mg each (Shimadzu Corporation, Universal
testing machine UH-10A, tablet size of 9.5 mm ϕ ,
compression pressure of 9.8 kN/cm²).

15 Example 8

A 900 g portion of manidipine hydrochloride, 1374.8
g of granulated lactose powder (Freund Sangyo.: Dilactose
S, mean particle diameter of 80 μ m), 301.5 g of
crospovidone, and 211.5 g of corn starch (Japan Corn
20 Starch) were placed in a fluidized bed granulating dryer
(Fuji Sangyo Co., Ltd., FD-5S type), and 4500 g of
purified water containing 225 g of hydroxypropylcellulose
(Nippon Soda Co., Ltd.) and 2.3 g of yellow ferric oxide
was sprayed, followed by granulating and drying processes,
25 to give granules G. The granules G were sized at the

screen size (1.0 mm ϕ) by a power mill (Showa Kagaku Kikai Kosakusho, P-3), to give sized granules G.

Separately, 2856 g of D-mannitol (Towa Chemical Industry Co., Ltd.: Mannit S), 1650 g of D-mannitol (Merck Co.: 1.05980), and 249 g of crospovidone were placed in a fluidized bed granulating dryer (Fuji Sangyo Co., Ltd., FD-5S type), and 1500 g of purified water containing 150 g of D-mannitol (Towa Chemical Industry Co., Ltd.: Mannit S), 7.5 g of yellow ferric oxide, and 37.5 g of anhydrous citric acid was sprayed, followed by granulating and drying processes, to give granules H. The granules G were sized at the screen size (1.0 mm) by a power mill, to give sized granules H.

A 737 g portion of sized granules G, 1815 g of sized granules H, 151.3 g of crystalline cellulose, 5.5 g of aspartame, and 41.3 g of magnesium stearate were mixed. This mixed powder was tableted into tablets weighing 250 mg each (Kikusui Seisakusho, Correct 12HUK, tablet size of 9.5 mm ϕ , compression pressure of 7.4 kN /cm²).

Example 9

A 44 g portion of manidipine hydrochloride, 442.4 g of trehalose (Asahi Chemical Industry Co., Ltd.: Trehalose P, mean particle diameter of 44 μ m), and 33 g of crospovidone were placed in a fluidized bed

granulating dryer (Powrex Co., LAB-1 type), and 231 g of purified water containing 11 g of hydroxypropylcellulose was sprayed, followed by granulating and drying processes, to give granules.

5 A 459.4 g portion of the granules, 27.2 g of crystalline cellulose, 1.0 g of aspartame, and 7.4 g of magnesium stearate were mixed.

10 This mixed powder was tabletted into tablets weighing 250 mg each (Kikusui Seisakusho, Correct 19KAWC, tablet size of 9.5 mm ϕ , compression pressure of 2.9 kN/cm²).

Example 10

15 Trehalose (Asahi Chemical Industry Co., Ltd.: Trehalose G, mean particle diameter of 346 μ m) was pulverized with a power mill (Showa Kagaku Kikai Kosakusho, P-3) at the screen size (0.5 mm ϕ), to give a powder with the mean particle diameter of 185 μ m.

20 This pulverized trehalose was used in place of the trehalose in Example 9, and processed under the same conditions as those in Example 9, to give tablets.

Example 11

25 Erythritol (Nikkenn Chemicals Co., Ltd.: mean particle diameter of 474 μ m) was pulverized with a power

mill (Showa Kagaku Kikai Kosakusho, P-3) at the screen size (0.5 mm ϕ), to give a powder with the mean particle diameter of 178 μ m.

This pulverized erythritol was used in place of the trehalose in Example 9, and processed under the same conditions as those in Example 9, to give tablets. (compression pressure 7.4 kN/cm²)

Example 12

Xylitol (Towa Chemical Industry Co., Ltd.: Xylit XC, mean particle diameter of 363 μ m) was pulverized with a power mill (Showa Kagaku Kikai Kosakusho, P-3) at the screen size (0.5 mm ϕ), to give a powder with the mean particle diameter of 135 μ m.

A 50 g portion of manidipine hydrochloride, the pulverized xylitol, 37.5 g of crospovidone, 15.6 g of crystalline cellulose, and 9.4 g of magnesium stearate were mixed.

This mixed powder was tabletted into tablets weighing 250 mg each (Shimadzu Corporation, Universal testing machine UH-10A, tablet size of 9.5 mm ϕ , compression pressure of 14.7 kN /cm²).

Example 13

A 50 g portion of manidipine hydrochloride, maltitol

(LESYS of Towa Chemical Industry Co., Ltd., mean particle diameter of 181 μm), 37.5 g of crospovidone, 15.6 g of crystalline cellulose, and 9.4 g of magnesium stearate were mixed.

5 This mixed powder was tabletted into tablets weighing 250 mg each (Shimadzu Corporation, Universal testing machine UH-10A, tablet size of 9.5 mm ϕ , compression pressure of 9.8 kN /cm²).

10 Example 14

Erythritol (Nikkenn Chemicals Co., Ltd.: mean particle diameter of 474 μm) was pulverized with a jet mill (Nippon Pneumatic MFG Co., Ltd., PJM-100SP), to give a powder with the mean particle diameter of 75 μm .

15 This pulverized erythritol was used in place of the trehalose in Example 9, and processed under the same conditions as those in Example 9, to give tablets.

Example 15

20 Sorbitol (Sorbitol DP-50M of Towa Chemical Industry Co., Ltd., mean particle diameter of 172 μm) was pulverized with a jet mill (Nippon Pneumatic MFG Co., Ltd., PJM-100SP), to give a powder with the mean particle diameter of 43 μm .

25 A 25 g portion of manidipine hydrochloride, the

pulverized sorbitol, 18.8 g of crospovidone, 7.8 g of crystalline cellulose, and 4.7 g of magnesium stearate were mixed.

5 This mixed powder was tabletted into tablets weighing 125 mg each (Shimadzu Corporation, Universal testing machine UH-10A, tablet size of 8.5 mm ϕ , compression pressure of 2.9 kN /cm²).

Comparative Example 1

10 D-Mannitol with the mean particle diameter of 21 μ m (Merck Co.: 1.05988) was used in place of the D-mannitol in Example 1, and processed under the same conditions as those in Example 1, to give tablets.

15 Comparative Example 2

D-Mannitol with the mean particle diameter of 21 μ m (Merck Co.: 1.05988) was used in place of the D-mannitol in Example 5, and processed under the same conditions as those in Example 5, to give tablets.

20

Comparative Example 3

Trehalose (Asahi Chemical Industry Co., Ltd.: Trehalose G) was pulverized with the atomizer (Fuji Paudal Co., Ltd., KII-2), to give a powder with the mean
25 particle diameter of 19 μ m.

This pulverized trehalose was used in place of the trehalose in Example 9, and processed under the same conditions as those in Example 9, to give tablets.

5 The results of measurement of the hardness and the intraoral disintegration time of the tablets obtained in the Examples and Comparative Examples by the above-mentioned test methods, and the results of evaluation of productivity based on the observation of fluidity, binding property, and adhesion of powder to the surface
10 of the punch during production of tablets are summarized in Table 1.

Table 1

Productivity, hardness, and intraoral disintegration time
of tablets

	Tabletting pressure (kN/cm ²)	Fluidity during tabletting	Binding property	Adhesion to punch	Hardness (N)	Intraoral disintegration time (second)
Example 1	9.8	good	absent	absent	37	25
Example 2	4.9	good	absent	absent	17	17
	9.8	good	absent	absent	39	16
	19.6	good	absent	absent	50	20
Example 3	9.8	good	absent	absent	24	17
Example 4	9.8	good	absent	absent	25	24
Example 5	9.8	good	absent	absent	26	19
Example 6	9.8	good	absent	absent	26	13
Example 7	9.8	good	absent	absent	33	25
Example 8	7.4	good	absent	absent	29	22
Example 9	2.9	good	absent	absent	21	52
Example 10	2.9	good	absent	absent	16	43
Example 11	7.4	good	absent	absent	36	31
Example 12	14.7	good	absent	absent	16	61
Example 13	9.8	good	absent	absent	21	51
Example 14	2.9	good	absent	absent	17	38
Example 15	2.9	good	absent	absent	16	67
Comparative Example 1	9.8	insufficient	present	present	49	26
Comparative Example 2	9.8	insufficient	present	present	33	21
Comparative Example 3	2.9	insufficient	present	present	25	36

5 INDUSTRIAL APPLICABILITY

Quickly disintegrating solid preparations,
preferably intraorally quickly disintegrating solid
preparations, more preferably intraorally quickly
disintegrating tablets of the invention obtained by the

THE NEW YORK PUBLIC LIBRARY
ASTOR LENOX TILDEN FOUNDATIONS
455 FIFTH AVENUE
NEW YORK

CLAIMS

1. A quickly disintegrating solid preparation comprising a) an active ingredient, b) a saccharide or sugar alcohol with the mean particle diameter of 30 μm to 300 μm , c) a disintegrating agent, and d) a cellulose compound.

2. The preparation according to claim 1, which is an intraorally quickly disintegrating solid preparation.

3. The preparation according to claim 1, which is a tablet preparation.

4. The preparation according to claim 1, which contains 40 to 95 parts of a saccharide or sugar alcohol per 100 parts of the solid preparation by weight.

5. The preparation according to claim 1, which contains 0.5 to 15 parts of a disintegrating agent per 100 parts of the solid preparation by weight.

6. The preparation according to claim 1, which contains 0.5 to 40 parts of a cellulose compound per 100 parts of the solid preparation by weight.

7. The preparation according to claim 1, wherein the saccharide is one or more saccharides selected from the group consisting of glucose, fructose, lactose, sucrose, and trehalose.

8. The preparation according to claim 1, wherein the saccharide is lactose.

9. The preparation according to claim 1, wherein the sugar alcohol is one or more sugar alcohols selected from the group consisting of D-mannitol, erythritol, xylitol, maltitol, and sorbitol.

5 10. The preparation according to claim 1, wherein the sugar alcohol is D-mannitol.

10 11. The preparation according to claim 1, characterized in that D-mannitol with the mean particle diameter of 30 μm to 300 μm is used as the saccharide or sugar alcohol with the mean particle diameter of 30 μm to 300 μm .

15 12. The preparation according to claim 1, wherein the disintegrating agent is one or more disintegrating agents selected from the group consisting of carmellose calcium, carboxymethylstarch sodium, croscarmellose sodium, and crospovidone.

20 13. The preparation according to claim 1, wherein the cellulose compound is one or more cellulose compounds selected from the group consisting of crystalline cellulose, powder cellulose, low substituted hydroxypropylcellulose, and carmellose.

14. The preparation according to claim 1, wherein the active ingredient is manidipine hydrochloride.

25 15. The preparation according to claim 1, wherein the active ingredient is voglibose.

16. The preparation according to claim 1, wherein the active ingredient is candesartan cilexetil.

17. The preparation according to claim 1, wherein the active ingredient is pioglitazone hydrochloride.

5 18. The procedure for production of the preparation according to claim 1, characterized in that a mixture containing a) an active ingredient, b) a saccharide or sugar alcohol with the mean particle diameter of 30 μm to 300 μm , c) a disintegrating agent, and d) a cellulose
10 compound is subjected to compression molding.

19. A quickly disintegrating solid preparation comprising a) an active ingredient, b-1) a saccharide or sugar alcohol with the mean particle diameter of 5 μm to below 90 μm , b-2) a saccharide or sugar alcohol with the
15 mean particle diameter of 90 μm to 500 μm , c) a disintegrating agent, and d) a cellulose compound.

20. The preparation according to claim 19, which contains 0.1 to 10 parts of the ingredient b-2) per 1 part of the ingredient b-1) by weight.

20 21. The preparation according to claim 19, characterized in that a mixture of the ingredient b-1) and the ingredient b-2) is used as the ingredient b-1) and the ingredient b-2).

22. The preparation according to claim 21, wherein
25 the mean particle diameter of the mixture is 30 μm to 300

μm.

23. The preparation according to claim 19, wherein the mean particle diameter of the ingredient b-1) is 30 μm to below 90 μm.

5 24. The preparation according to claim 19, wherein the mean particle diameter of the ingredient b-1) is 35 μm to 80 μm.

10 25. The preparation according to claim 19, wherein the mean particle diameter of the ingredient b-2) is 90 μm to 300 μm.

26. The preparation according to claim 19, wherein the mean particle diameter of the ingredient b-2) is 90 μm to 200 μm.

15 27. The preparation according to claim 19, wherein the saccharide is one or more saccharides selected from the group consisting of glucose, fructose, lactose, sucrose, and trehalose.

28. The preparation according to claim 19, wherein the sugar is lactose.

20 29. The preparation according to claim 19, wherein the sugar alcohol is one or more sugar alcohols selected from the group consisting of D-mannitol, erythritol, xylitol, maltitol, and sorbitol.

25 30. The preparation according to claim 19, wherein the sugar alcohol is D-mannitol.

31. The preparation according to claim 19,
characterized in that D-mannitol with the mean particle
diameter of 30 μm to below 90 μm and D-mannitol with the
mean particle diameter of 90 μm to 300 μm are used as the
5 ingredient b-1) and the ingredient b-2), respectively.

32. The procedure for production of the preparation
according to claim 19, characterized in that a mixture
containing a) an active ingredient, b-1) a saccharide or
sugar alcohol with the mean particle diameter of 5 μm to
10 below 90 μm , b-2) a saccharide or sugar alcohol with the
mean particle diameter of 90 μm to 500 μm , c) a
disintegrating agent, and d) a cellulose compound is
subjected to compression molding.

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

☐ Original ☐ Supplemental ☐ Substitute ☒ PCT ☐ Design

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: QUICKLY DISINTEGRATING SOLID PREPARATIONS

of which is described and claimed in:

- ☐ the attached specification, or
☐ the specification in the application Serial No. _____ filed _____;
 and with amendments through _____ (if applicable), or
☒ the specification in International Application No. PCT/JP00/03923, filed June 16, 2000, and as amended on _____ (if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, ' 1.56.

I hereby claim priority benefits under Title 35, United States Code, ' 119 (and ' 172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Japan	172532/1999	June 18, 1999	Yes


I hereby claim the benefit under Title 35, United States Code ' 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code ' 112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, ' 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; and Michael S. Huppert, Reg. No. 40,268, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys and agents named herein to accept and follow instructions from AOYAMA & PARTNERS, as to any action

to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

Direct Correspondence to Customer No:  000513 PATENT TRADEMARK OFFICE	Direct Telephone Calls to: WENDEROTH, LIND & PONACK, L.L.P. 2033 "K" Street, N.W., Suite 800 Washington, D.C. 20006-1021 Phone (202) 721-8200 Fax (202) 721-8250
--	---

Full Name of First Inventor	FAMILY NAME <u>OHKOUCHI</u>	FIRST GIVEN NAME <u>Kazuhiro</u>	SECOND GIVEN NAME
Residence & Citizenship	CITY <u>Toyonaka-shi</u>	STATE OR COUNTRY <u>Japan</u>	COUNTRY OF CITIZENSHIP <u>Japan</u>
Post Office Address	ADDRESS <u>7-15, Eirakuso 1-chome, Toyonaka-shi, Osaka, Japan</u>	CITY	STATE OR COUNTRY ZIP CODE

Full Name of Second Inventor	FAMILY NAME <u>KOYAMA</u>	FIRST GIVEN NAME <u>Hiroyoshi</u>	SECOND GIVEN NAME
Residence & Citizenship	CITY <u>Mishima-gun</u>	STATE OR COUNTRY <u>Japan</u>	COUNTRY OF CITIZENSHIP <u>Japan</u>
Post Office Address	ADDRESS <u>2-20-204, Wakayamadai 2-chome, Shimamoto-cho, Mishima-gun, Osaka, Japan</u>	CITY	STATE OR COUNTRY ZIP CODE

Full Name of Third Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY ZIP CODE

Full Name of Fourth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY ZIP CODE

I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1st Inventor Hagahiro Ohkouchi Date 2001/09/14
2nd Inventor Hiroyoshi Iiyama Date 2001/09/14
3rd Inventor _____ Date _____
4th Inventor _____ Date _____

The above application may be more particularly identified as follows:

U.S. Application Serial No. _____ Filing Date _____

Applicant Reference Number _____ Atty Docket No. _____

Title of Invention _____
